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14. ABSTRACT

This report describes the fourth year of work on the award "Proton Therapy Dose Characterization and Verification" which includes investigation in the following areas: (A) the use of positron emission tomography (PET) to determine the dose deposited by a therapeutic proton beam, (B) studies of the radiobiological effect of proton therapy, and (C) support for matching patients to clinical trials. This report also covers the third year of a continuation award "Development of Technology for Image-Guided Proton Therapy" that focuses on transferring technology currently in conventional radiotherapy systems to the proton treatment rooms, especially that technology related to daily patient localization. A component of both of these awards also supports the work done by the Walter Reed Army Medical Center scientists. That work is reported in grant #W81XWH-04-2-0022.

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Introduction

The overall goal of this multi-year research project in collaboration with the Walter Reed Army Medical Center is to develop the necessary technology to make the proton facility that is under construction in Philadelphia the most advanced proton radiotherapy center. Award # W81XWH-07-2-0121 comprises phases 4 and 5 of this endeavor and consists of the following projects:

Phase 4

A. Positron Emission Tomography (PET) of proton beams to verify dose deposition

1. PET Detector Development: Design a PET scanner optimized for the application of verifying the dose distribution deposited by proton therapy beams. This includes detector selection, electronic and mechanical engineering, data acquisition, and reconstruction software.
2. Cross-section measurements: Measure positron-emitting isotope production from the primary elements found in tissue and compare to the GEANT4 Monte Carlo simulation program.
3. Determination of elemental composition: The verification of the dose distribution cannot be done directly because the production of isotopes is not easily related to the dose deposited. Instead a Monte Carlo simulation program is used to calculate both dose deposited and isotopes produced and the latter is compared to the measured value. It is critical that the correct elemental composition be used in the simulation for this comparison to work. We are investigating how additional imaging methods, such as dual-energy CT, can help determine the composition.

B. Radiobiology and microdosimetry of proton beams

1. Radiobiology studies in the proton beam: Develop techniques to measure the radiobiological effectiveness of the proton beam.
2. Microdosimetry studies in the proton beam: Build proportional chambers to measure the linear energy transfer in a proton therapy field.

Phase 5

A. Apply state-of-the-art localization methods, including cone-beam CT and

B. implanted radiofrequency beacons, currently used in conventional radiotherapy to proton radiotherapy.

C. Develop a computer program to maximize the efficiency of the proton facility.

Body

The Hospital of the University of Pennsylvania, in collaboration with Walter Reed Army Medical Center, is building the most advanced cancer treatment facility in the world. This will be a fully-integrated facility utilizing state-of-the-art imaging and conformal treatment techniques including proton radiotherapy. Research projects with the intent of full implementation of end products are required to reach the full potential of proton therapy. In the original statement of work first of five planned projects were identified, to be implemented on a yearly basis to provide the most advanced cancer treatment facility in the world. Each of these projects will help advance proton therapy worldwide and result in measurable benefits. The projects identified were:

(1) Multi-leaf collimator (MLC) for use on proton therapy gantries

(2) Cone Beam CT on the Gantry for localization of target volumes

(3) Proton Radiography to determine dose and stopping power of various tissues

(4) Positron Emission Tomography (PET) imaging on the gantry to evaluate dose deposition within tissues irradiated

(5) Scanning proton beam using adaptive radiotherapy techniques based on implementation of MLC, Cone Beam CT, PET imaging.

A major aim of the entire project is to provide the most advanced radiation therapy to military personnel and their immediate families; the facility opened for patient treatment in January, 2010.

Much of this work has been initiated in earlier phases of this award. Phase 1 concentrated on designing and building a Multi-leaf collimator for use in proton therapy. Phase 2 focused on studying the optimal way to use scanned proton beams. The purpose of Phase 3 was to include the ideas of adaptive radiotherapy techniques and to define the role of imaging in proton therapy including the introduction of on-gantry cone beam CT (CBCT). The integration of these techniques, redefined as image guided proton therapy (IGPT) and adaptive proton therapy (APT) was a major aim of the phase 3 proposal.

This report concentrates on the fourth year progress on the project titled “Proton Therapy Dose Characterization and Verification” and the third year of progress on the award “Development of Technology for Image-Guided Proton Therapy”. The Statement of Work in the approved grant proposals included the following items to be investigated. (Note: to minimize confusion, the years in which we expected to perform the work have been replaced by the fiscal year because there are several separate starting dates.)

Phase 4 Scope of Work

Year 1 ending 9/30/2008	• Develop PET detectors • Identify and develop appropriate model systems for preclinical testing proton RBE in the Penn proton beam facility • Assemble equipment and develop data analysis software • Install and test tablet PCs
Year 2 ending 9/30/2009	• Design PET scanner • Design mechanical gantry • Develop data acquisition and electronics • Develop image reconstruction algorithm • Test and implement cell lines and methods as defined in task 9 with standard photon radiation • Build and test tissue-equivalent proportional counters
Year 3 ending 9/30/2010	• Characterize the performance of the PET instrument • Measure positron-emitting isotope production • Use dual-energy CT and MRI to determine the composition of materials
Year 4 ending 9/30/2011	• Measurement of RBE for protons using the Penn proton beam facility • Measure LET for scattered and scanned beams • Enter forms on tablet PCs

Phase 5 Scope of Work

Year 1 ending 9/30/2009	• Identify a vendor consortium to develop a solution for CBCT on or near the gantry • Develop a set of hardware and software specifications for the CBCT system • Develop a timeline and detailed cost breakdown for the CBCT project consistent with the clinical needs of the UPHS/WRAMC proton therapy project • Evaluate radiation hardness of electronics used in the Calypso localization system • Measure radiation field in a proton gantry room that the Calypso will experience • Develop deterministic and stochastic models for beam allocation • Conduct robustness test for deterministic and stochastic models

Year 2 ending 9/30/2010	• Install a prototype Calypso system in the gantry room and test at regular intervals while measuring integral neutron dose • Determine how the Calypso beacons affect the dose distribution using Monte Carlo simulations and measurement • Develop model for patient scheduling • Conduct robustness test for the combined model • Implement production models and deploy models and protocols
Year 3 ending 9/30/2011	• Install CBCT system in gantry room and test using phantoms

Progress

The work over the past year is divided into the following sections:

Phase 4

A. Positron Emission Tomography (PET) of proton beams to verify dose deposition

1. PET Detector Development: A prototype PET detector has been constructed with data acquisition hardware and software.
2. Cross-section measurements: The Monte Carlo simulation code has been adapted to generate positron emitting isotopes at levels consistent with published measurement results.

B. Radiobiology and microdosimetry of proton beams

1. Techniques to measure the radiobiological effectiveness of the proton beam have been developed and tested in x-ray beams. Much of the equipment to perform these measurements has been installed in the proton facility.
2. Microdosimetry studies in the proton beam: Build proportional chambers to measure the linear energy transfer in a proton therapy field.

Phase 5

A. Develop a cone-beam CT that can be used in a proton treatment room

It has proven difficult to find a vendor that can co-develop this system at a reasonable cost.

B. Adapt the Calypso localization system for proton rooms

A great deal of progress was made in the area of making Calypso more radiation hardened so it could function in the proton treatment rooms.

C. Beam allocation and scheduling program

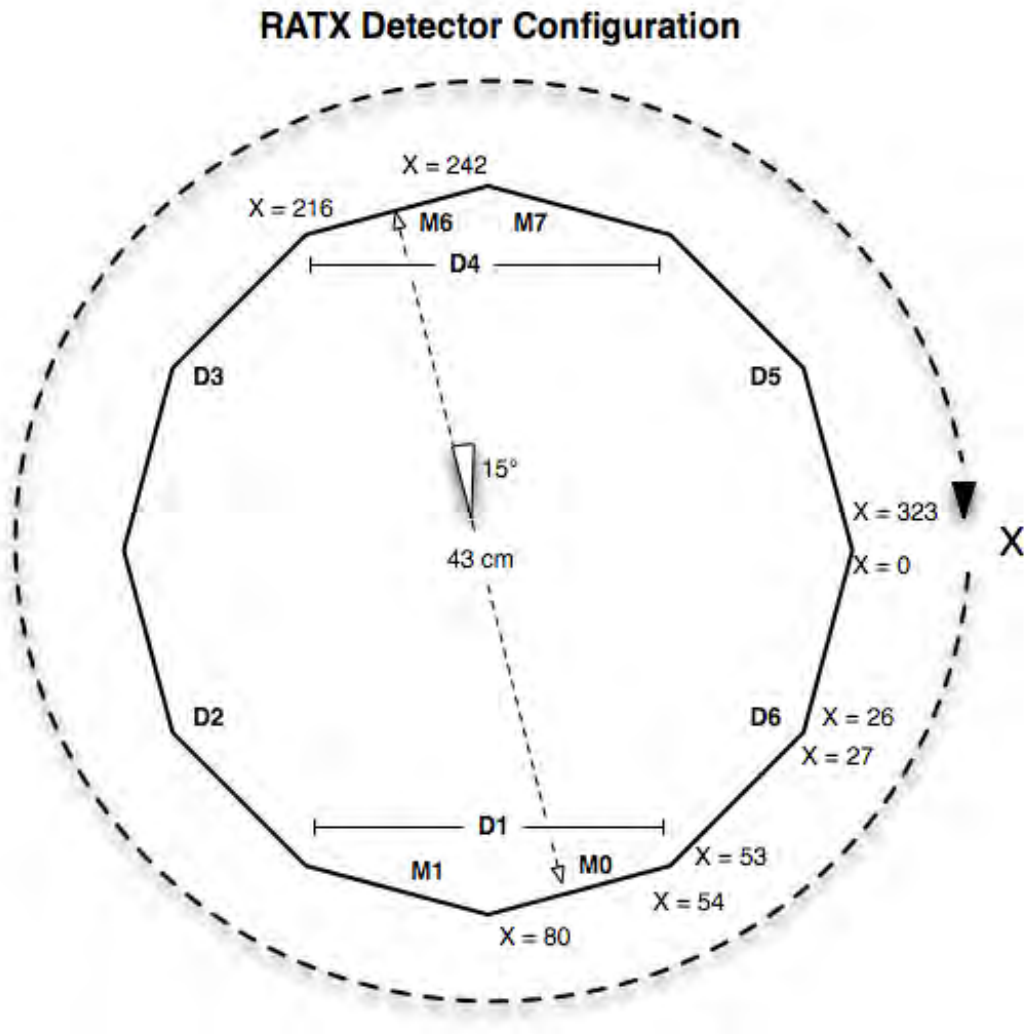
The conceptual design of this program is complete and we are awaiting a fully functional facility to provide the data required to complete and test it.

4.A. PET progress

1. Detector Development

A.1 Experimental Set-up

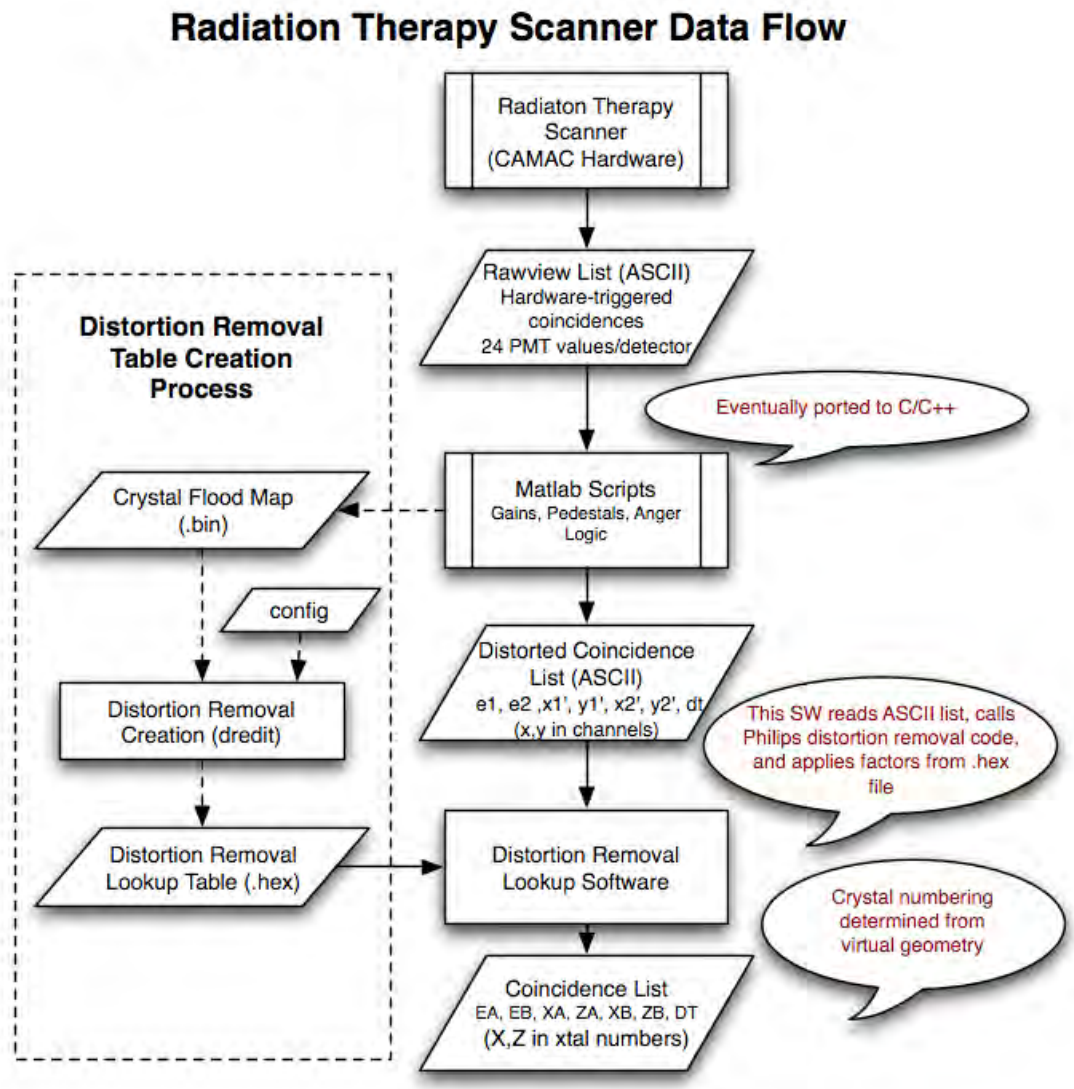
In this past year we have developed an integrated approach to acquire and process data with the proto-type detector that we have developed, such that it builds upon our group's established data format and image reconstruction workflow and fits within our standard scanner geometry paradigm. While this paradigm is normally used to describe a continuous, polygonal ring of detectors, it has the flexibility to treat a two-detector system as two modules that are part of such a ring which happens to be incomplete. This description also allows us to add more modules after the fact without making changes to the data format from the original modules. As an example, see the diagram below. In this configuration, the detector is described as a 12-sided polygon, where each side is a detector module. The two



proton therapy modules would occupy the opposing sides designated for module M0 and

module M6, and the crystal numbering within each detector would correspond to those modules. That is, M0 would contain crystal X-positions from 54 through 80, and M6 will contain X = 216 through 242. Data described in this way, when passed through our existing processing software, would appear to come from a complete ring that received no data from the other 10 modules.

A sensitivity image would then be used to inform the software that it should expect no data other than from M0 and M6, and this could be updated if more detectors are added. Also, the diameter of the virtual ring can be made arbitrarily large if more detector separation is needed. This would appear as a polygonal scanner with large gaps between modules, which is a scenario already handled by our software. If desired detector separation would result in apparent overlap of the virtual polygon sides, a fewer-sided polygon should be chosen for the geometry.



Data from the scanner initially comes from CAMAC hardware and written to an ASCII-formatted list file. The conversion of this data to a format that is supported by the existing software and fits into the geometric paradigm described above, is achieved in the "distortion removal" process which corrects for the non-linear positioning of the Anger logic. First a distortion removal file is created using detector flood data. This file uses a standard format that is compatible with Philips and Penn software, and it maps the raw output positions of the CAMAC hardware into the crystal numbering scheme shown in the above diagram. This file is then used as input to distortion removal software which takes the ASCII list as input and writes out distortion-corrected listmode data in a coincidence list format used by Philips and Penn. The image reconstruction program has already been developed to read these list data, and generate an image. See the flow chart below.

4.B. Radiobiology and microdosimetry

1. Radiobiology

In this year, we have continued our experiments comparing the radiosensitivity of Head and Neck Cancer cells with plateau vs mid-SOBP protons (Fig 1).

During the year, we finished analyzing SQ20b radioresistant and had begun analyzing the radiation response of the more radiosensitive HNC cell lines FaDu and MSK-1. These experiments show that, contrary to our previously stated hypothesis, these highly radioresistant cells do not display a dramatic difference in radiosensitivity for the plateau vs mid-SOBP portions of the proton depth dose distribution (**Fig 2-3**).

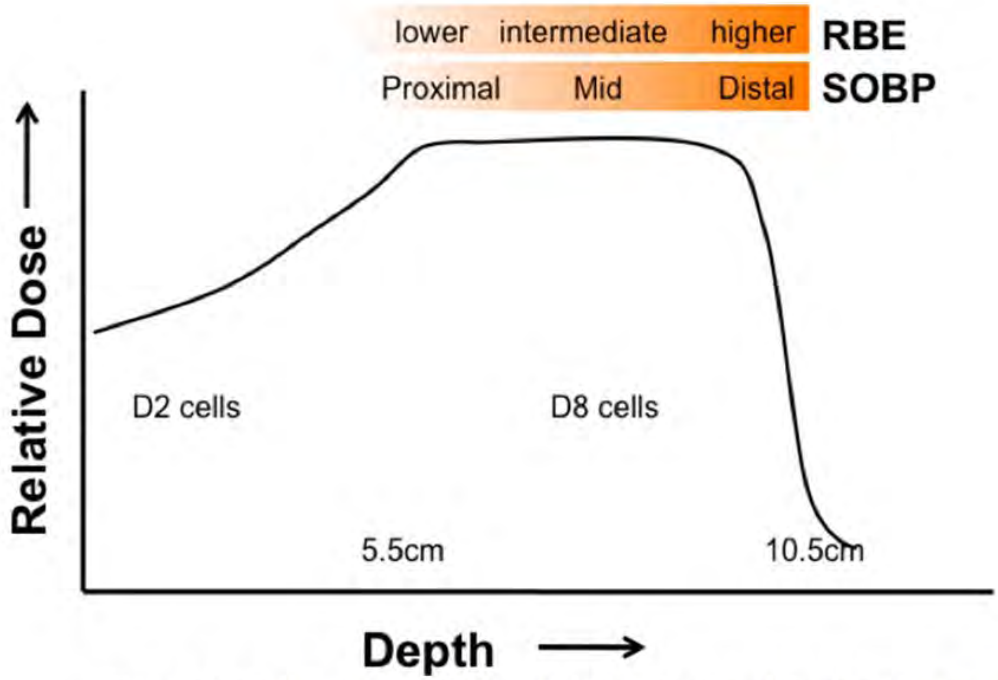


Figure 1: Cells were positioned at the 2 cm and 8 cm water equivalent thickness in a 10.5 cm range, 5 cm modulated SOBP.

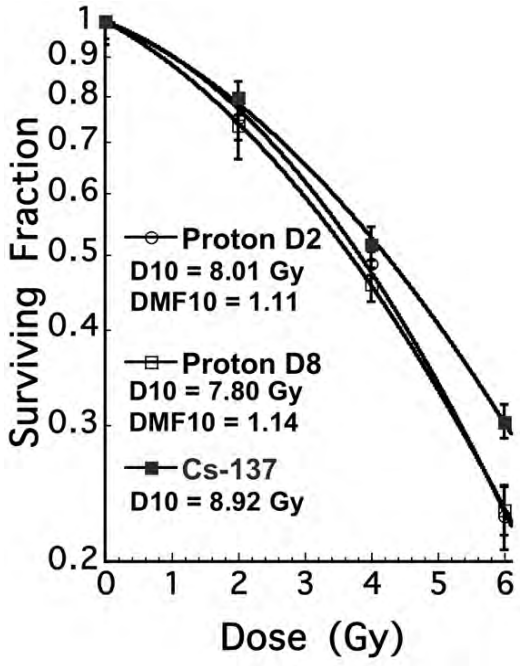


Figure 2: Radiosensitivity of SQ20b cells in high and intermediate LET proton regions. Clonogenic survival experiments were performed as described in methods and results are presented as mean +- SEM for experiments performed in triplicate on separate days.

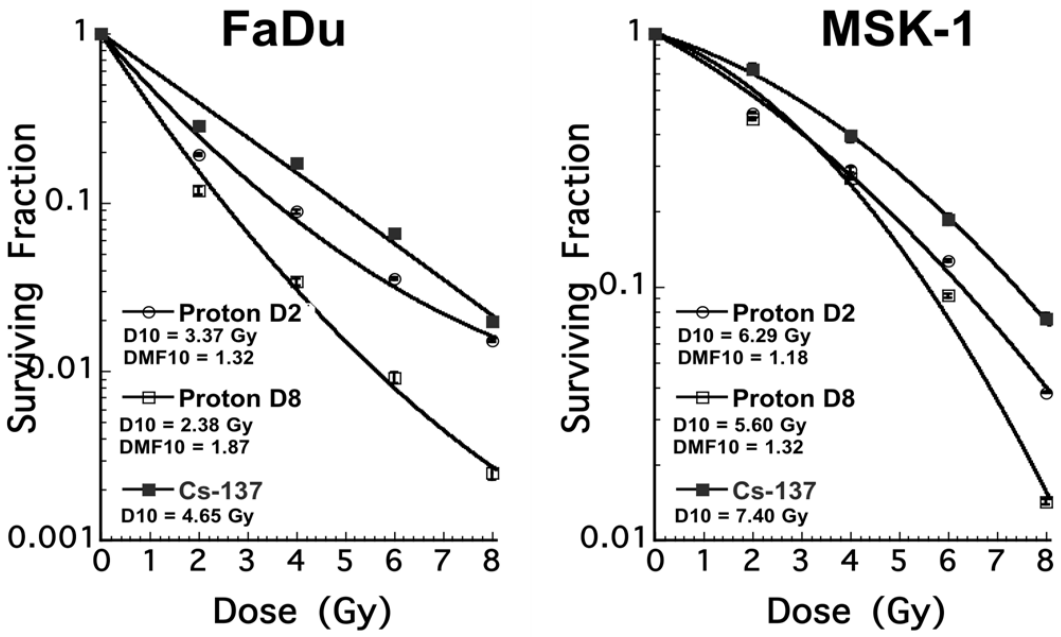


Figure 3: Radiosensitivity of FaDu and MSK-1 cells in high and intermediate LET proton regions. Clonogenic survival experiments were performed as described in methods and results are presented as mean +- sd for experiments performed with a minimum of 6 replicate plates per condition irradiated on the same day.

We have attempted to replicate the results with FaDu and MSK-1. Unfortunately, due to technical difficulties with the incubator system, the baseline plating efficiencies were inconsistent, leading to results that could not be interpreted. A repeat of these studies is currently planned. We have also sought to determine whether the surprising lack of radiosensitization of SQ20b by increasing LET was due to contributions of the EGFR-Ras-Pi3k radioresistance pathway. In these experiments, we performed clonogenic survival experiments in the presence and absence of erlotinib, an EGFR pathway inhibitor.

In these experiments, cells were pre-treated for 1h prior to irradiation with the EGFR inhibitor erlotinib or vehicle (control) and irradiated using a double scattered proton beam and a 10.5 cm range, 5 cm modulated SOBP (Figure 1). These positions were chosen to measure the RBE in the pleateu and mid-SOPB portions of the dose distribution and the particle fluence was adjusted for each to give final doses of 2, 4 or 8 Gy (note that this is measured in J/kg of protons or photons, not CGE) for each depth. On the same day, clonogenic survival was performed using a LINAC source using cells obtained from the same culture flasks. The percentage of surviving cells was calculated by normalizing the percentage of cells forming colonies at a particular radiation dose relative to the percentage of cells forming colonies without irradiation. A linear-quadratic approximation of cell survival Is presented for comparison of SQ20bcells with or without Erlotinib from previous experiments. Note that the erlotinib did not radiosensitize the LINAC treated cells to the same extent previously observed. There was, however, a differential in the radiosensitization

between low (D2) and high (D8) LET protons. These experiments need to be replicated under conditions where the erlotinib provides a greater degree of radiosensitization to the control (LINAC) cells (Figure 4). However, these preliminary data suggest that there may the contributions of EGFR radioresistance pathway signaling to cellular radiosensitivity may be greater for higher LET radiation. Conversely, these experiments suggest caution should be advised when combining radiosensitizing chemotherapy/targeted therapy with proton radiation in patients.

In the next quarter, we will continue to work to extend these observations to determine whether the molecular determinants of radiosensitivity in photon radiation translate to uniform (scalable) changes in radiosensitivity for protons with different LET.

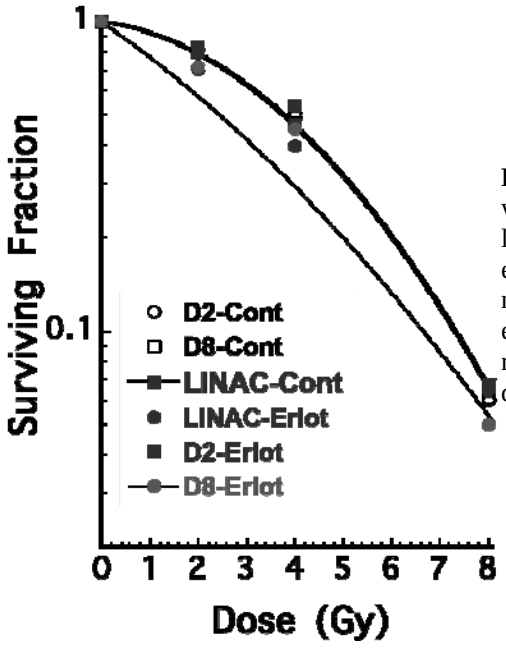


Figure 4: Radiosensitivity of SQ20b cells with or without the EGFR inhibitor Erlotinib in high and low LET proton or photons. Clonogenic survival experiments were performed as described in methods and results are presented as mean +- sd for experiments performed with a minimum of 6 replicate plates per condition irradiated on the same day.

2. Microdosimetry

As a part of our effort to produce and publish a manuscript on the secondary neutron measurements using the dual ionization chamber technique, we have conducted detailed Monte Carlo simulations of the ionization chambers that were constructed in quarters past. The goal of these simulations was to address a potential weak point in the dual chamber technique, which is knowledge of the neutron sensitivity of our chambers and how it may vary with neutron energy spectrum and measurement geometry relative to the secondary neutron source located within the tungsten MLC. The neutron energy spectrum has been

obtained from prior simulations of the secondary neutrons produced by protons incident on the MLC.

Both the tissue equivalent (TE) and Magnesium (Mg) chamber geometry were created within the Geant4 Monte Carlo code and placed within a 30cm x 30cm x 30cm water phantom where both narrow (3mm diameter) and broad (5cm diameter) beams of neutrons with energies from 0-300 MeV were simulated to be incident on the center of the chamber's active volume. Subsequently, dose was scored within the active volume for each type of chamber as well as the dose to water in the absence of a chamber, Fig. 1 and 2. The sensitivity of the chambers to neutron radiation was determined based on the known number of simulated incident neutrons and the dose deposition, Fig. 3 and 4. Published experimental data of the neutron sensitivity of a commercially available Mg chamber is shown in Fig. 5. This data is tabulated as a function of mean neutron energy with the neutron energy spectrum for any specific data point consisting of a broad range energies in contrast to the simulations where the sensitivity can be calculated as a function of discrete neutron energies. Comparison of the simulated Mg chamber neutron sensitivity with experimental data at neutron energy of 50 MeV shows a similar result (sensitivity ~0.3). However, lower energies show variation between experiment and simulation with the simulated sensitivity falling to around 0.2 and the experimental sensitivity falling well below 0.05 to 0 as the neutron energy drops to 0 MeV. A more detailed analysis can be carried out to compare the experimental sensitivity of the mean neutron energy with the simulation by accumulating the Monte Carlo sensitivity spectrum over the neutron energy spectrum used for the respective experimental data point in the cases where this energy spectrum is known.

The unknown variables of neutron energy spectrum and beam geometry can contribute to discrepancies between simulated and experimental chamber sensitivities therefore further efforts to determine the chamber sensitivity through simulation will be delayed until the manuscript describing our measurements of secondary neutron dose is completed. The simulations and comparisons with previously published experimental data will likely form an additional manuscript.

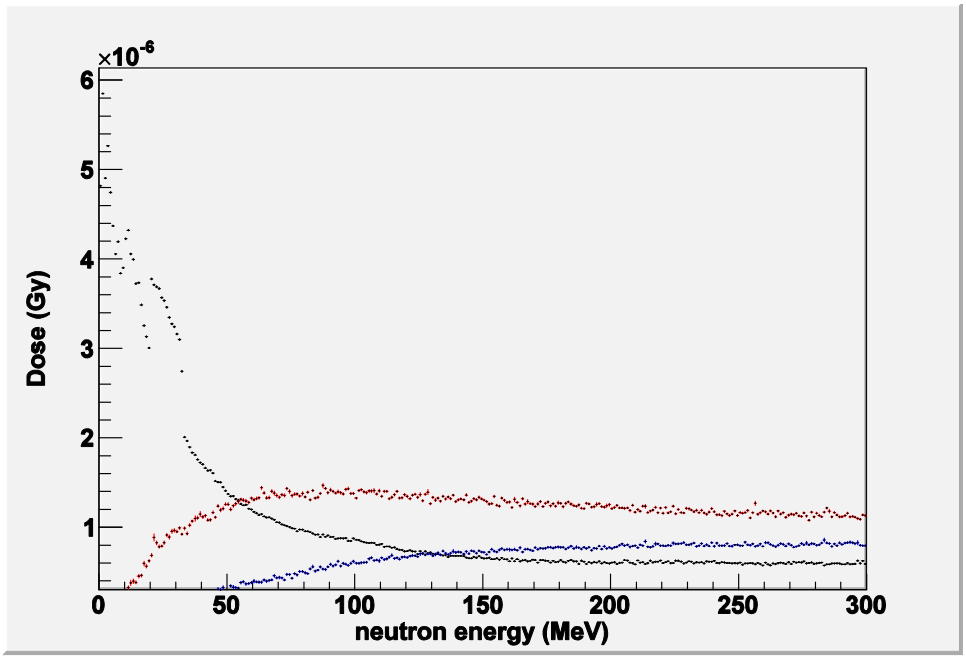


Figure 1. Neutron dose in Water (black), TE(red), and Mg(blue) chambers as a function of incident neutron energy for a narrow 3mm beam.

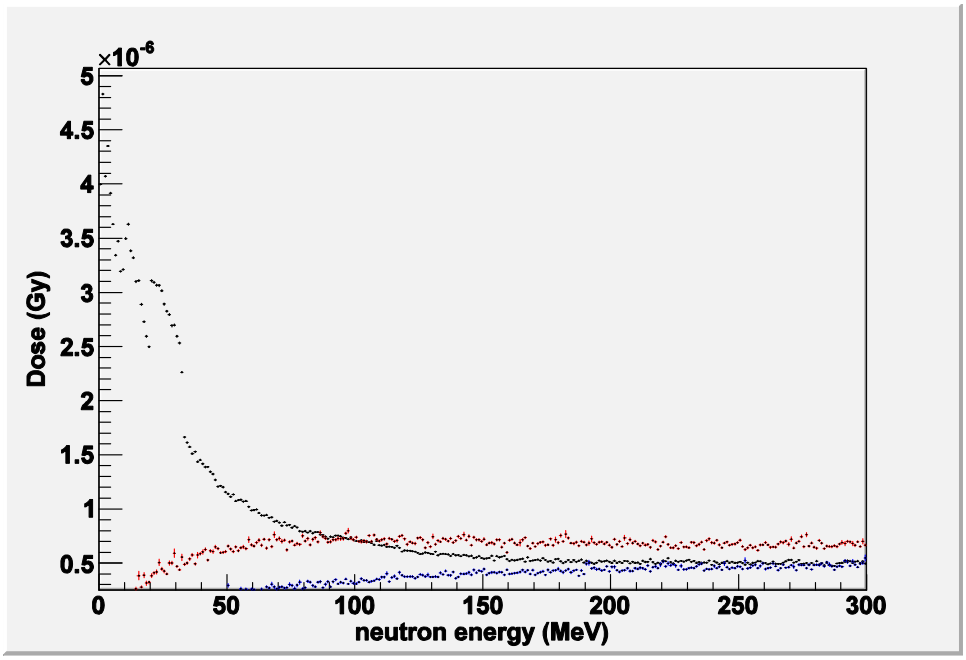


Figure 2. Neutron dose in Water(black), TE(red), and Mg(blue) chambers as a function of incident neutron energy for a broad 5cm beam.

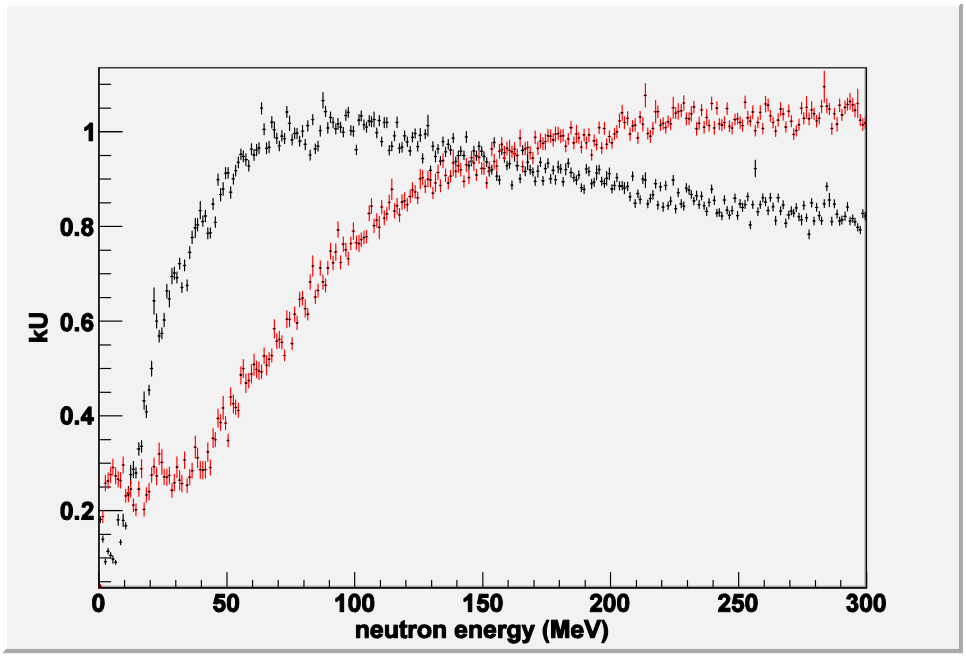


Figure 3. The neutron sensitivity, kU, for TE(black) and Mg(red) chambers as a function of incident neutron energy for a narrow 3mm beam.

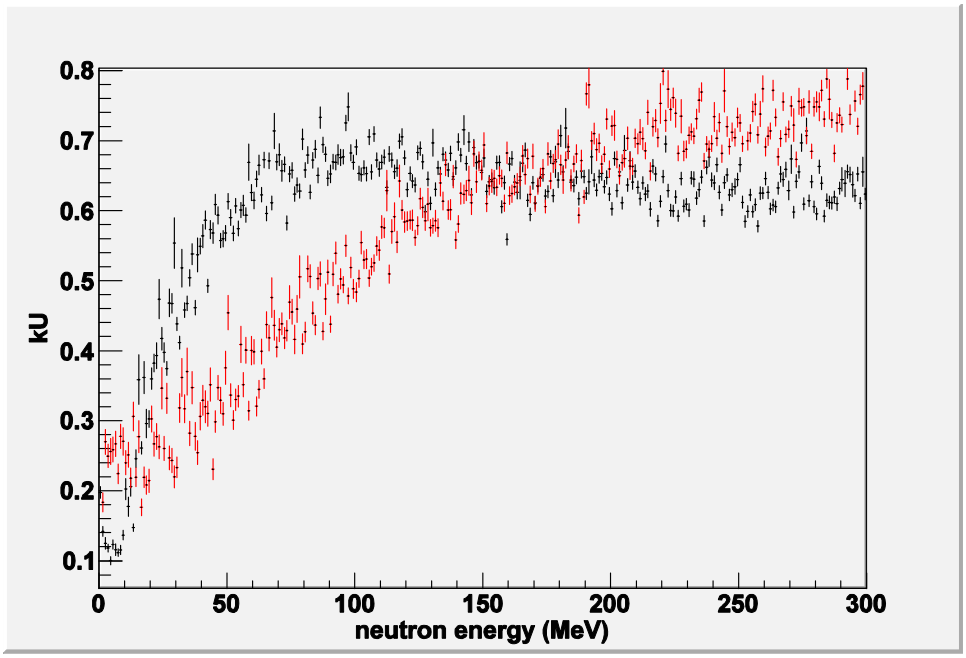


Figure 4. The neutron sensitivity, kU, for TE(black) and Mg(red) chambers as a function of incident neutron energy for a broad 5cm beam.

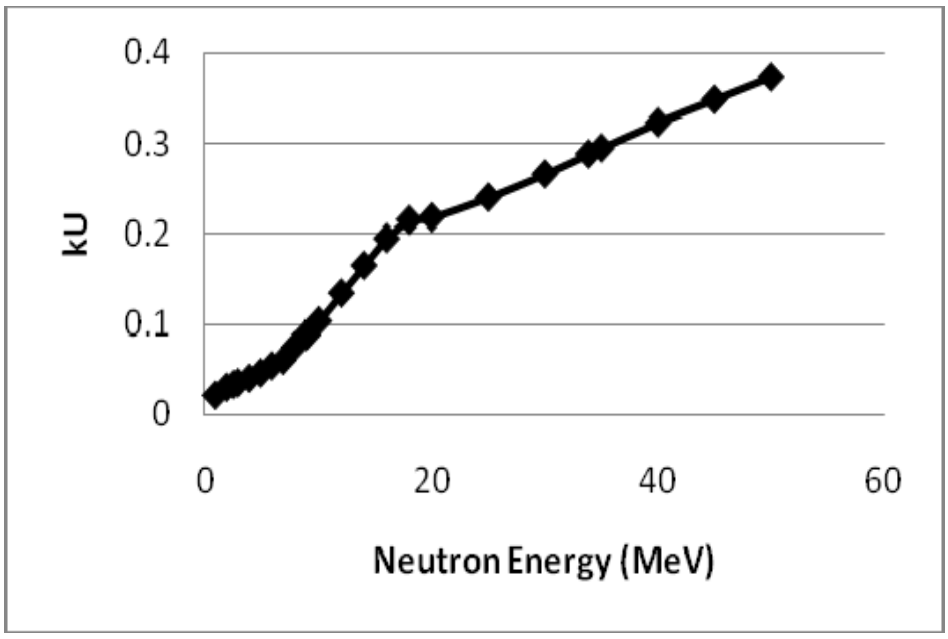


Figure 5. Experimental data showing the neutron sensitivity, kU, for a commercial Mg chamber as a function of mean neutron energy (Waterman *et. al*., 1979).

Phase 5

A. CBCT project

We are considering a development project with our proton vendor (IBA) that would result in a cone-beam CT using the x-ray tubes and panels that are already in our treatment rooms. This development would upgrade the x-ray tube to an oil-cooled one but otherwise would be mainly software changes. The major risk in this approach is that the long arms that hold the x-ray detector panels will not be in a predictable position as the gantry rotates thus degrading the resolution of the reconstructed image.

Early attempts to adapt the CBCT of a conventional vendor did not work out.

B. Implanted RF beacons (Calypso)

During the past year Calypso has redesigned their system based on the testing done at the University of Washington neutron beam facility. They believe they have resolved the problems caused by radiation damage and are now preparing to install a system in our facility. This system would be used to test reliability and accuracy but will not be used clinically.

C. Beam allocation and patient scheduling project

This part of the project has been in a holding pattern because the next step, after development of the algorithms that we described previously, is to make measurements under realistic conditions to collect the parameters that will be fed into the program. Because we just started treating patients in four rooms few months ago and are about to start treating patients in the fifth rooms we are not yet at the point where the operations are able to give the appropriate data. We expect that after some upgrades to IBA software near the end of 2011 and during 2012 we will be able to collect that data and progress with the development of the algorithm and testing it.